REMARKS

Claim 74 has been amended. Claims 74-93 are pending in the present application.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance. Reconsideration of the application in view of the above amendments and the following remarks is requested.

I. The Rejection of Claims 74-93 under 35 U.S.C. § 112

Claims 74-93 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description. The Office Action states:

> The limitations introduced to the end of claim 74 starting with "wherein the mRNA processing stabilizing sequence is foreign to the consensus promoter " do not appear to have support in the specification. Hence, for examination purposes said amendment to claim 74 is considered to be new matter.

This rejection is respectfully traversed.

Applicant has amended claim 74 to recite: "wherein the "consensus" promoter is constructed from any promoter which can function in the *Bacillus* cell". Page 8, lines 11-17, of the specification provides that "[t]he construction of a "consensus" promoter may be accomplished by site-directed mutagenesis to create a promoter which conforms more perfectly to the established consensus sequences for the "-10" and "-35" regions of the vegetative "sigma A-type" promoters for *Bacillus subtilis* (Voskuil *et al.*, 1995, *Molecular Microbiology* 17: 271-279). The consensus sequence for the "-35" region is TTGACA and for the "-10" region is TATAAT. The consensus promoter may be obtained from any promoter which can function in a *Bacillus* host cell." Examples of naturally occurring promoters from which consensus promoters can be constructed are provided on page 8, lines 18, to page 9, line 9. Since the consensus promoters are constructed from naturally occurring promoters, the consensus promoters are necessarily foreign to the mRNA processing stabilizing sequence.

For the foregoing reasons, Applicant submits that the rejections under 35 U.S.C. § 112 have been overcome. Applicant respectfully requests reconsideration and withdrawal of the rejection.

II. The Rejection of Claims 74-77, 80, 82-84, 86-88, and 91-93 under 35 U.S.C. § 103

Claims 74-77, 80, 82-84, 86-88, and 91-93 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Hung *et al.* (*Mol. Gen. Genet.* 219: 129-136, 1989) in view of Lereclus *et al.* (WO 94/25612). The Office Action states:

> [T]he examiner respectfully disagrees with the applicant that Lereclus provides no unequivocal evidence that its cryIIIa downstream region can be used with other promoters that are foreign to said "downstream region" to enhance recombinant gene expression. This is because in column 2 of U.S. patent 6,140,104 (also cited by the applicant as the U.S. patent corresponding/equivalent to Lereclus French patent) Lereclus teaches that the promoter used in his constructs may be both endogenous and exogenous to the host used (see column 2) so long as it is functional. Furthermore, with respect to "downstream region" Lereclus also indicates that apari form the exact sequences of the "downstream region" those that can hybridize thereto, under non-stringent conditions may be used (see column 60) suggesting flexibility in compositions of "downstream region (which could inherently originate from other species) that may be utilized in its constructs. Therefore in view of said evidence, in contrast to applicant's view one of ordinary skill in the art is motivated in combining promoters which may be foreign to said "downstream region" or homologs thereof with a reasonable expectation of obtaining enhanced expression of genes in bacillus and even some other hosts (as disclosed in column 9 of Lereclus U.S. patent.

This rejection is respectfully traversed.

The Examiner has the initial burden of establishing a *prima facie* case of obviousness. A finding of obviousness under § 103 requires a determination of the scope and content of the prior art, the differences between the claimed invention and the prior art, the level of ordinary skill in the art, and whether the differences are such that the claimed subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Graham v. Deere, 383 US 1 (1966).

Under 35 U.S.C. § 103, the law requires, when relying on a combination of prior art references to render a claimed invention obvious, that the prior art references contain within them a suggestion of the possibility of achieving the improvement of the claimed invention, such a suggestion being either express or implied. In re Sernaker, 217 USPQ 1 (Fed. Cir. 1983). Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination. Carella v. Starlight Archery, 231 USPQ 644 (Fed. Cir. 1986); In re Stencel, 828 F2d 751, 4 USPQ2d 1071 (Fed. Cir. 1987). It is also impermissible to use the claims as a framework from which to pick and choose among individual references to recreate the

claimed invention. In re Fine, 5 USPQ2d 1596 (Fed. Cir. 1988). A reference, or references, must show or suggest the properties and results of the claimed invention, or suggest the claimed combination as a solution to a given problem, in order to successfully be relied upon for an obviousness rejection. In re Wright, 6 USPQ2d 1959 (Fed. Cir. 1988). The mere fact that prior art references could be readily modified to form the claimed invention is not sufficient either, since the mere fact that the prior art could be modified would not make the modification obvious unless the prior art suggests the desirability of the modification. In re Laskowski, 10 USPQ2d 1397 (Fed. Cir. 1989). Applicant maintains its position that the references cited by the Examiner do not contain the requisite teaching, and therefore cannot be combined to support the obviousness rejections of the present claims.

Hung *et al.* teach a *Bacillus subtilis* cell comprising a DNA construct comprising a consensus *bla* promoter originated from *E. coli*, having the sequence TTGACA for the -35 region and TATAAT for the -10 region operably linked to a mouse dihydrofolate reductase (DHFG) encoding gene. Hung *et al.* do not teach or suggest a DNA construct further comprising an mRNA processing/stabilizing sequence.

Lereclus *et al.* teach an expression system comprising a CryIIIA gene, under the control of a *cryIIIA* promoter as well as a *cryIIIA* sequence called the "downstream region" or a "mRNA processing/stabilizing sequence", situated between the promoter and the coding sequence to be expressed and susceptible of acting at the post-transcriptional level during gene expression.

The Office argues that it would have been obvious to one of ordinary skill in the art to start with the DNA construct of Hung and place the "downstream region" and optionally, *cryIIIA* gene of Lereclus into said construct in order to successfully express either the mouse dihydrofolate reductase encoding gene or *Bacillus thuringiensis cryIIIA* gene in all *Bacillus* cells. The Office also argues that one of ordinary skill in the art is motivated in combining promoters which may be foreign to said "downstream region" or homologs thereof with a reasonable expectation of obtaining enhanced expression of genes in bacillus and even some other hosts (as disclosed in column 9 of Lereclus U.S. patent). Applicant respectfully disagrees.

Lereclus *et al.* on page 9, lines 14-21, of WO 94/25612 (see U.S. Patent No. 6,140,104 for English translation) state:

> As to the nature of the promoter, it seems preferable to use a promoter derived from the host cell used for the expression of the gene of interest. However, in certain situations the use of an exogenous promoter may be indicated. For example, promoters such as the promoters of the degO, λPL, lacZ, cryI, cryIV or alpha-amylase genes may be used.

On pages 33-34 and Figure 5 of WO 94/25612, the expression data from pHT901'lacZ and pHT304'lacZ demonstrate that placing the *cryIIIA* "downstream region" downsteam of a heterologous promoter has no positive effect on expression of the *lacZ* gene. Based on the methods described in WO 94/25612 to construct these two plasmids, it is apparent that the promoter for the *lacZ* gene is indeed present and oriented such that the *lacZ* gene is expected to be transcribed from this promoter. Indeed, Figure 5 demonstrates low levels of lacZ expression in a strain harboring pHT304'lacZ. However, there is no evidence for improvement in a strain harboring pHT901'lacZ which has the *cryIIIA* "downstream region" situated downstream of the *lacZ* promoter. One of ordinary skill in the art would expect to see a significant improvement if, in fact, a heterologous promoter is able to function in association with the *cryIIIA* "downstream region" and Figure 5 does not support this assumption. While Lereclus *et al.* show in Figure 6 of WO 94/25612 that the pHT7902'lacZ construct (where the *cryIIIA* promoter is upstream of the *cryIIIA* "downstream region" which is upstream of the *lacZ* gene) increases expression of the *lacZ* gene relative to the pHT7907'lacZ construct (where the *cryIIIA* "downstream region" is absent), no evidence is presented that the *cryIIIA* "downstream region" can be used with other promoters that are foreign to the *cryIIIA* "downstream region" to increase expression of a gene. In fact, based on the results of Lereclus *et al.*, the *cryIIIA* "downstream region" appears to be specific for the *cryIIIA* promoter.

Applicant submits that the results of Lereclus showing that placing the *cryIIIA* "downstream region" downstream of the *lacZ* promoter has no positive effect on expression of the *lacZ* gene teaches away from using the *cryIIIA* "downstream region" with other promoters that are foreign to the *cryIIIA* "downstream region" to increase expression of a gene. Based on the Lereclus results, there is no reasonable expectation of success of using the *cryIIIA* "downstream region" with other promoters that are foreign to the *cryIIIA* "downstream region" to increase expression of a gene

Applicant submits, therefore, that the references cited by the Examiner do not contain the requisite teaching, and therefore cannot be combined to support the obviousness rejection of the present claims. Moreover, there is no motivation to inserting the "downstream region" of Lereclus *et al.* into the DNA construct of Hung *et al.* because there is no reasonable expectation of success of increasing expression of a gene based on the results obtained by Lereclus *et al.* wherein the mRNA processing/stabilizing sequence is foreign to the "consensus" promoter.

For the foregoing reasons, Applicant submits that the rejections under 35 U.S.C. § 103(a) have been overcome. Applicant respectfully requests reconsideration and withdrawal of the rejection.

III. The Rejection of Claims 89-90 under 35 U.S.C. § 103

Claims 89-90 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Hung *et al.* (*Mol. Gen. Genet.* 219: 129-136,1989) in view of Lereclus *et al.* (WO 94/25612) further in view of Jorgensen *et al.* (WO 93/10249) for the reasons of record. This rejection is respectfully traversed.

Hung *et al.* and Lereclus *et al.* are discussed in Section II above.

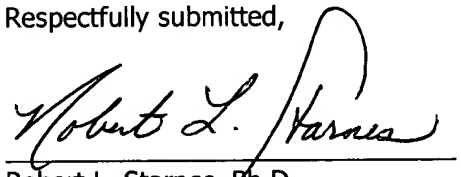
Jorgensen *et al.* disclose a *Bacillus* promoter derived from a variant of a *Bacillus licheniformis* alpha-amylase promoter for use in expressing heterologous genes.

For the reasons stated in Section II, Applicant submits that the rejections under 35 U.S.C. § 103(a) have been overcome. Applicant respectfully requests reconsideration and withdrawal of the rejection.

III. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,



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